USING COGNITIVE ASSESSMENT TOOLS REMOTELY TO DETECT MCI IN THE CONTEXT OF COVID AND POTENTIAL USE WITH ANTI-AMYLOID THERAPIES

Serge Gauthier, C.M., C.Q., MD, FRCPC

Emeritus Professor in Neurology and Psychiatry,
McGill University

POTENTIAL CONFLICTS OF INTEREST

Member of scientific advisory boards with Advantage Therapeutics, Alzheon, Amyriad Therapeutics, Biogen, Cerveau Technologies, Lundbeck, MoCA Test Inc., TauRx

CONCLUSIONS

- The diagnosis of MCI and dementia due to AD is becoming biological
- The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments
- MCI due to AD has become a target for disease modifying therapies

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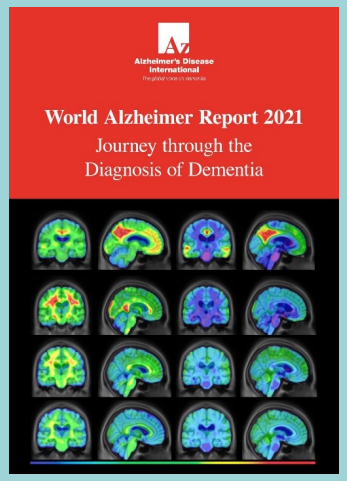
- The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments – possibly a golden age for remote cognitive screening for MCI
- MCI due to AD has become a target for disease modifying therapies and will require in-person and remote cognitive & functional follow-up



www.alzint.org/worldreport

Six sections:

- **Part I**: Clinical assessment
- **Part II**: Laboratory tests
- **Part III**: Personal testimonies
- **Part IV**: Formulation of diagnosis
- **Part V**: Particular circumstances
- **Part VI**: The future of the diagnosis of dementia

World Alzheimer Report 2021: Journey through the diagnosis of dementia

Expert essays: To encapsulate a broad range of knowledge, healthcare professionals were invited to submit essays within their field of expertise.

Surveys: The three surveys were conducted concurrently between March and June 2021, targeting people living with dementia and carers, clinician's and Alzheimer and dementia associations

Testimonies: Individual case studies were requested from people living with dementia and eight are included covering all WHO regions. A larger set of videos, accompanying this report can be found on ADI's YouTube channel

The report contains survey data from a total of 3,431 respondents consisting of:

- 1,111 multidisciplinary clinicians in 108 countries (62% from high income countries and 38% from low- and middle-income countries)
- 205 people with dementia and 2122 carers in 83 countries
- 101 Alzheimer's and dementia associations from around the world

The report contains survey data from a total of 3,431 respondents consisting of:

- 1,111 multidisciplinary clinicians in 108 countries (62% from high income countries and 38% from low- and middle-income countries)
- 205 people with dementia and 2122 carers in 83 countries
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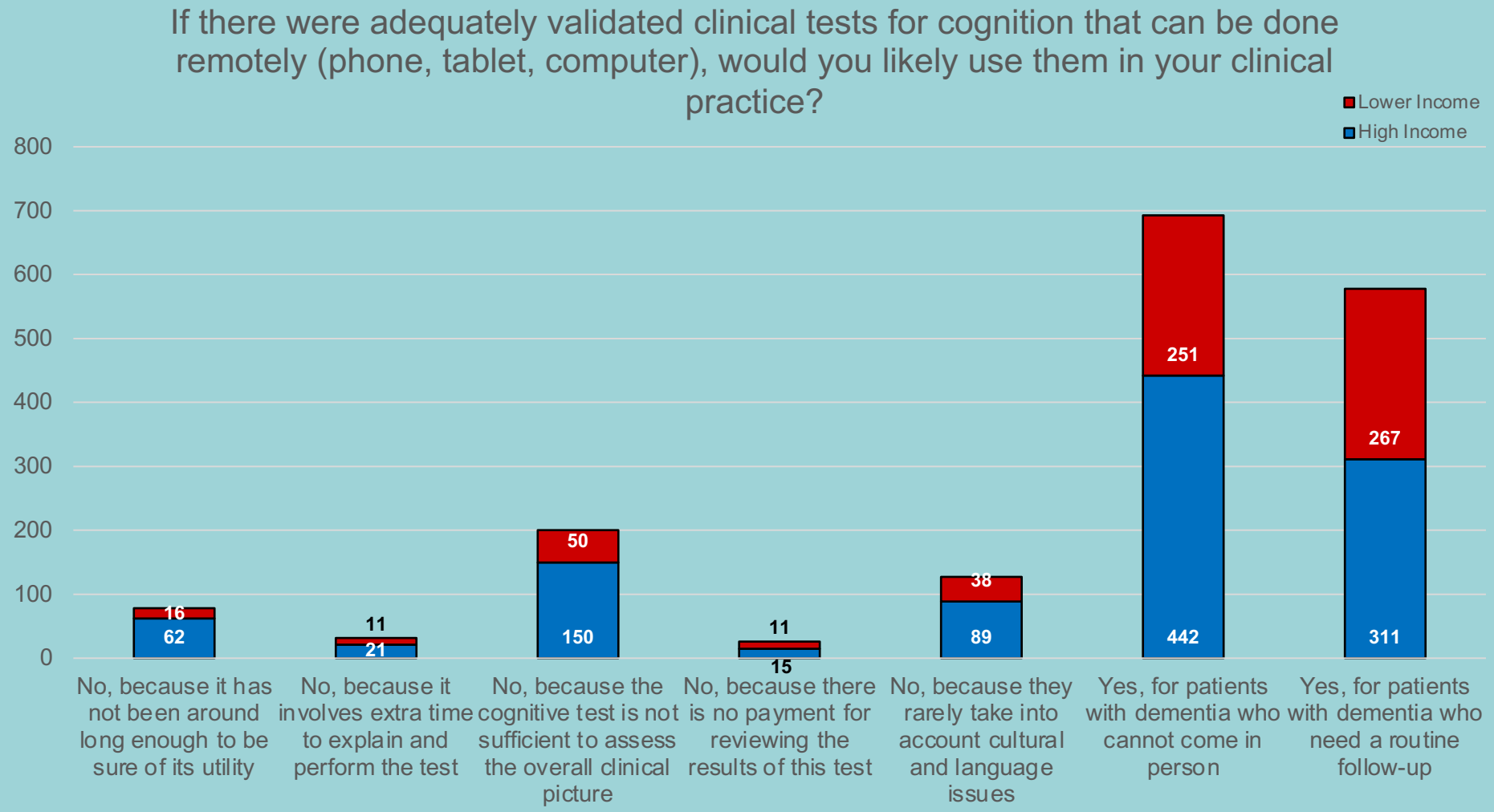
- Cognitive assessments are required for the diagnosis of dementia and to track changes over time.
- The cognitive screening tests most used by clinicians world-wide are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).
- Tests that overcome the influence of language differences are needed, such as the Visual Cognitive Assessment Test (VCAT).
- As a result of the COVID-19 pandemic, many clinicians have incorporated telemedicine into their practice

POLLING QUESTION NO 1: TRUE OR FALSE?

In the survey conducted among clinicians worldwide towards WAR2021 on the diagnosis of dementia, most answered that they do not want to use remote cognitive assessments


If there were adequately validated clinical tests for cognition that can be done remotely (phone, tablet, computer), would you likely use them in your clinical practice?
Lower Income
High Income
800
700
600
500
400
300
200
100
0
16
62
11
21
50
150
11
15
38
89
251
442
267
311
No, because it has not been around long enough to be sure of its utility
No, because it involves extra time to explain and perform the test
No, because the cognitive test is not sufficient to assess the overall clinical picture
No, because there is no payment for reviewing the results of this test
No, because they rarely take into account cultural and language issues
Yes, for patients with dementia who cannot come in person
Yes, for patients with dementia who need a routine follow-up

POLLING QUESTION NO 1: TRUE OR FALSE?

In the survey conducted among clinicians worldwide towards WAR2021 on the diagnosis of dementia, most answered that they do not want to use remote cognitive assessments

FALSE

Recommendations

- Better training, education and time allocation is required in primary healthcare in diagnosis, to combat lack of skills and confidence and to remove the counter-productive time pressure on primary care doctors when dealing with a complex and sensitive diagnosis and disclosure.

- Healthcare systems must invest in and improve diagnostic capabilities, moving towards precision diagnosis, to eradicate high levels of misdiagnosis.

Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer's disease

Plasma p-tau levels are increased in AD

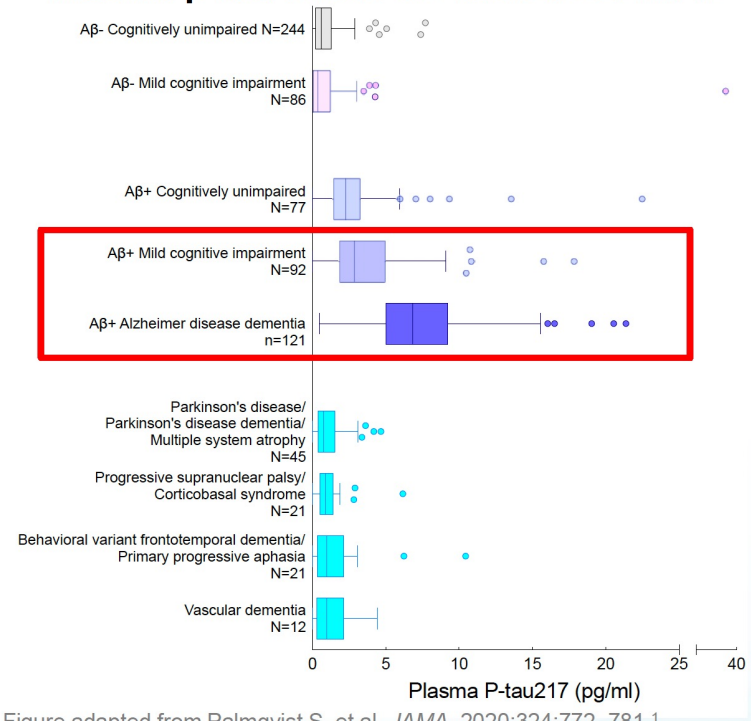


Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]

Approximative ordering of Alzheimer's disease biomarker changes during the disease course

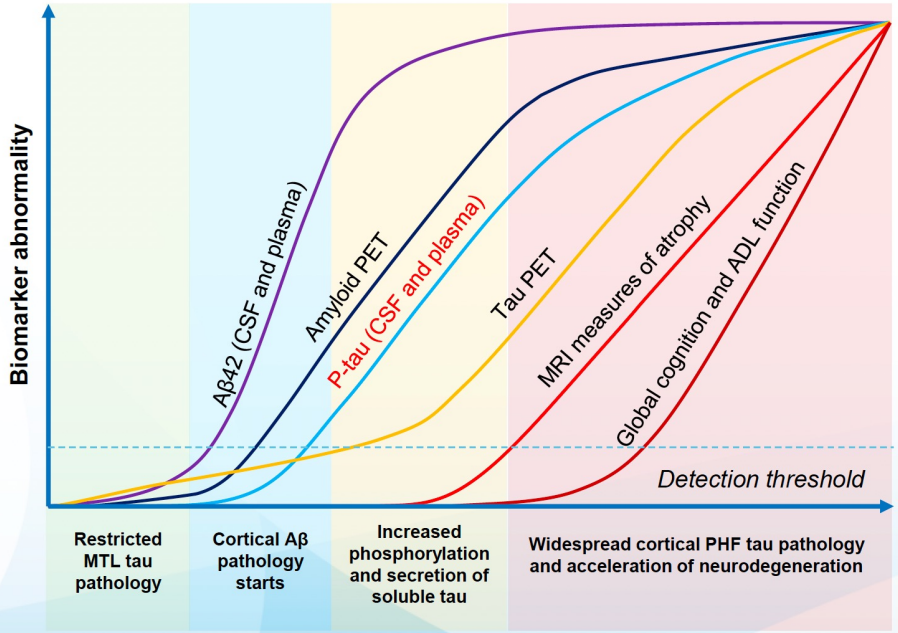


Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; MTL, medial temporal lobe; p-tau, phosphorylated tau; PET, positron emission tomography; PHF, paired helical filaments; t-tau, total tau. 1. Palmqvist S, et al. *JAMA*. 2020;324:772–781; 2. Hansson O. *Nat Med*. 2021;27:954–963.

Recommendations

- National awareness raising campaigns must address the stigma surrounding dementia, especially in some low-income countries where up to 90% of cases go undiagnosed and actively promote awareness of the warning signs, in line with action area two of the WHO Global action plan on dementia.

- Best practice in assessment must be recognised as a combination of cognitive testing, backed up by scan and/or CSF testing, plus preparedness and readiness to embrace emerging biomarkers.

- Improved access to scanner technology required for confirmatory diagnosis, for access to emerging treatments and ongoing monitoring, with equivalent specialist training.

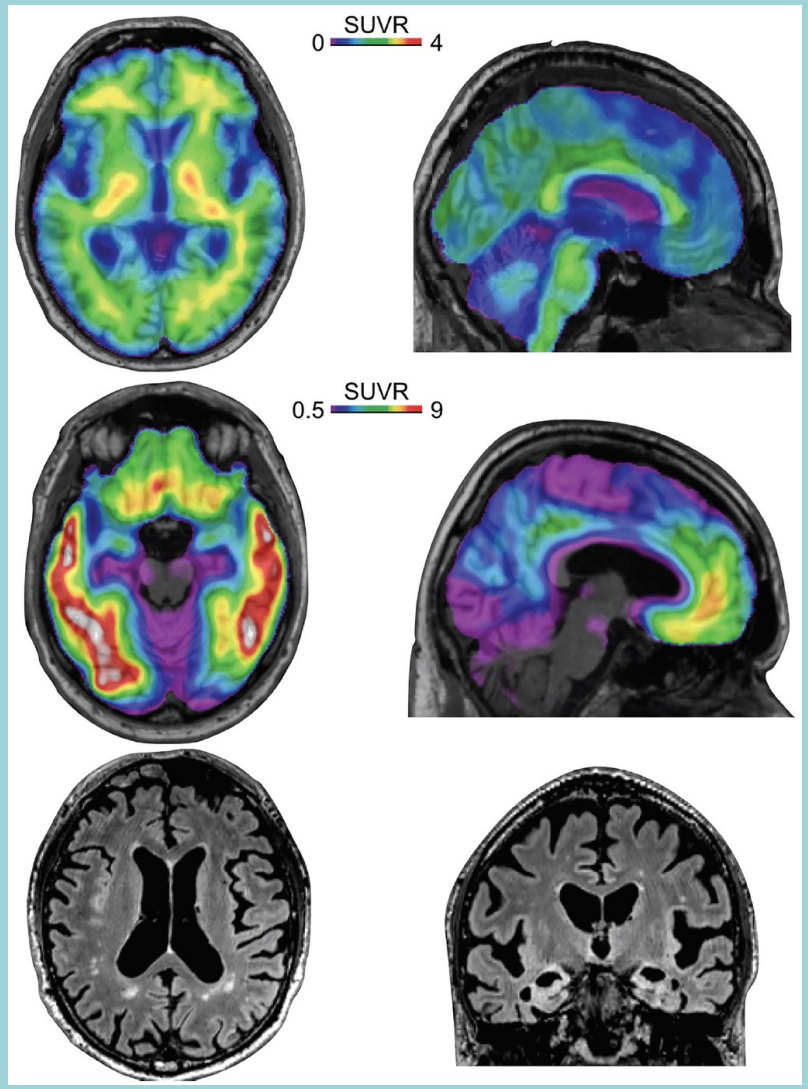


Figure. Amyloid positron emission tomography (PET), tau PET, and MRI from a man, age 80, with mild dementia (CDR 1) after a gradual cognitive decline over 5 years and clinical diagnosis of probable AD. The amyloid PET is read as negative, the tau PET positive on the temporal lobe, precuneus, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak V). The MRI shows mild general and hippocampal atrophy (Scheltens 4-5), White matter hyperintensities (WMH) are limited to the periventricular regions (Fazekas 1). This individual has a neurofibrillary tangle predominant dementia.

Recommendations

- Clinicians must become aware and better informed about information, support and planning available via national Alzheimer and dementia associations and the vital role they play in pre and post diagnostic support.

- Further build on the innovative, often technology-based approaches, including telemedicine, which evolved rapidly during the COVID-19 pandemic, and research how these might best supplement, but not replace, future cognitive assessment, while acknowledging the benefits for remote or rural communities or for those unable to travel safely.

alzheimer's association
AAIC 21

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Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

REVIEW ARTICLE

Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19

Maiya R. Geddes[1,2,3] | Megan E. O'Connell[4,5] | John D. Fisk[6,7,8] | Serge Gauthier[2] | Richard Camicioli[9] | Zahinoor Ismail[10,11] | for the Alzheimer Society of Canada Task Force on Dementia Care Best Practices for COVID-19

POLLING QUESTION NO 2: TRUE OR FALSE?

The same ethical principles apply to telemedicine and remote cognitive assessments as for in-person encounters.

alzheimer's association
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Ethical Considerations

- The same ethical principles apply to telemedicine and in-person encounters
- Ethical adoption of technology
- Fidelity: The interests and welfare of patient come first
- Verbal consent – Transparent disclosure of rationale and limitations
- Handling imminent risk
- Minimize obtrusiveness
  - Telephone vs videoconference
- Verbal and non-verbal cues conveying empathy
  - Clinician training

POLLING QUESTION NO 2: TRUE OR FALSE?

The same ethical principles apply to telemedicine and remote cognitive assessments as for in-person encounters.

TRUE

POLLING QUESTION NO 3: TRUE OR FALSE?

There are no functional and behavioral scales usable for remote assessments in MCI.

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Remote assessment of Affect, Behavior and Function

–**Neuropsychiatric symptoms** (e.g., Neuropsychiatric Inventory Questionnaire [NPI-Q]; Mild Behavioral Inventory Checklist [MBI-C])

–**Affect**

- Depression (e.g., Cornell Scale for Depression in Dementia [CSDD]; Patient Health Questionnaire-9 [PHQ-9])
- Anxiety (Rating Anxiety in Dementia [RAID] – sensitive; Penn State Worry Questionnaire - specific)

–**Function** (e.g., AD8; Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]; Quick Dementia Rating System; FAQ; Lawton-Brody IADL; 4-item IADL scale; Amsterdam IADL questionnaire)

–**Sleep** (e.g., Mayo Sleep Questionnaire)

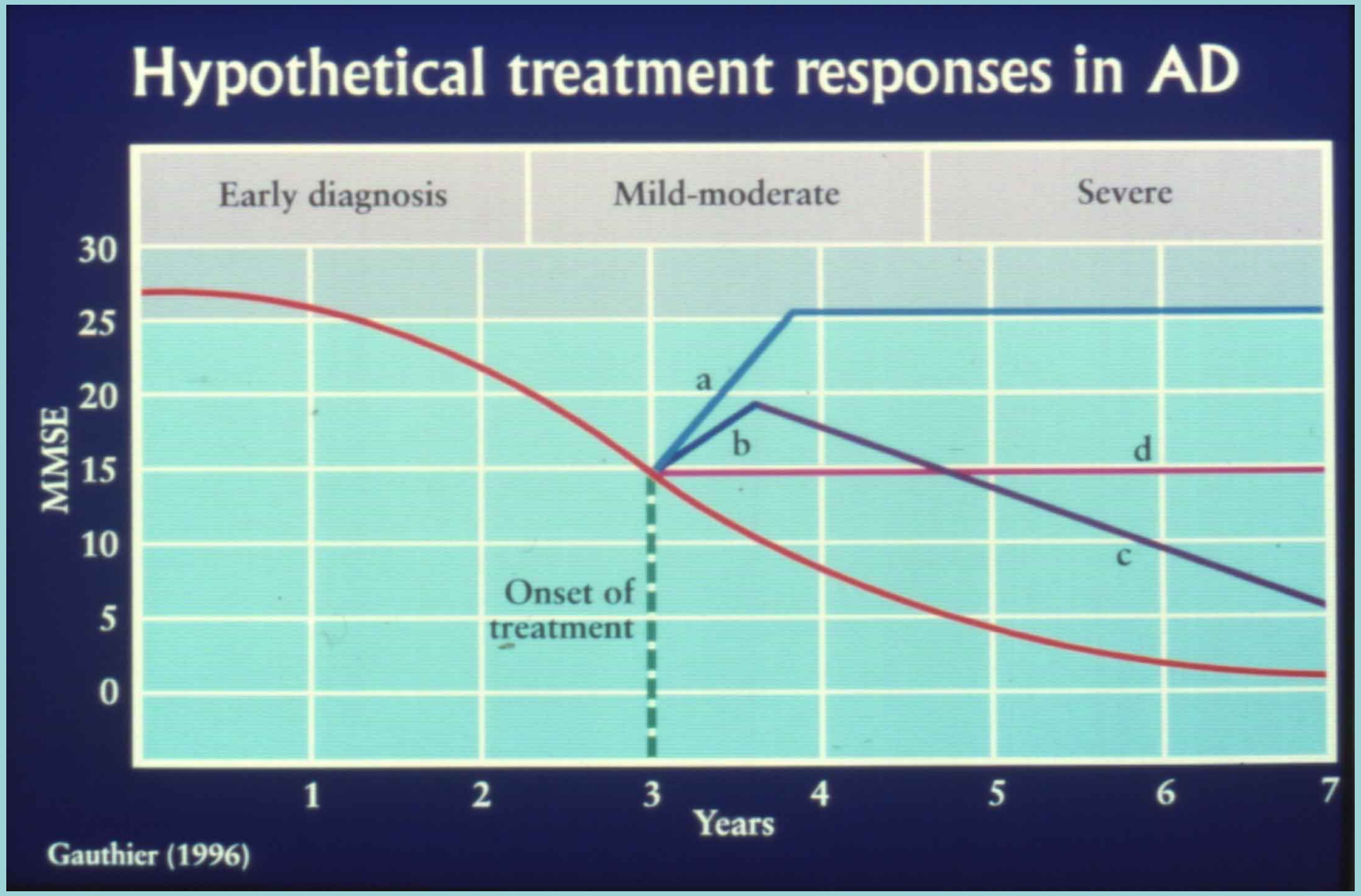
Geddes et al., 2020; Geddes et al., 2021 (accepted)

POLLING QUESTION NO 3: TRUE OR FALSE?

There are no functional and behavioral scales usable for remote assessments in MCI.

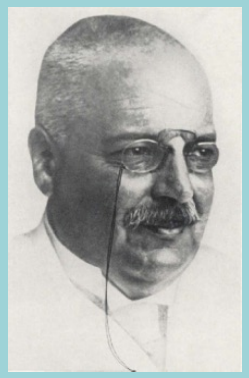
FALSE

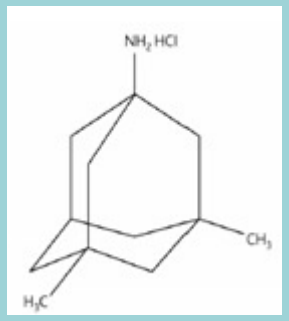
Hypothetical treatment responses in AD



Gauthier (1996)

Therapy in AD: The first hundred years and looking forward…….



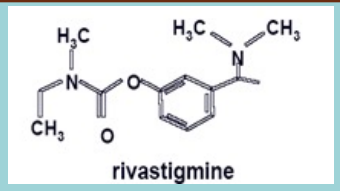


Memantine NMDA Uncompetitive Receptor Antagonist

1906 1910 1974 1982 1997 2004 2010 2021

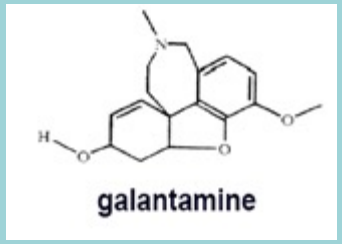
The cholinergic hypothesis

Acetylcholinesterase inhibitors

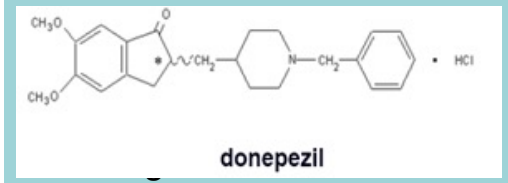


rivastigmine

First Disease Modifying Rx?
Amyloid and tau lowering?
Next generation targets?



galantamine

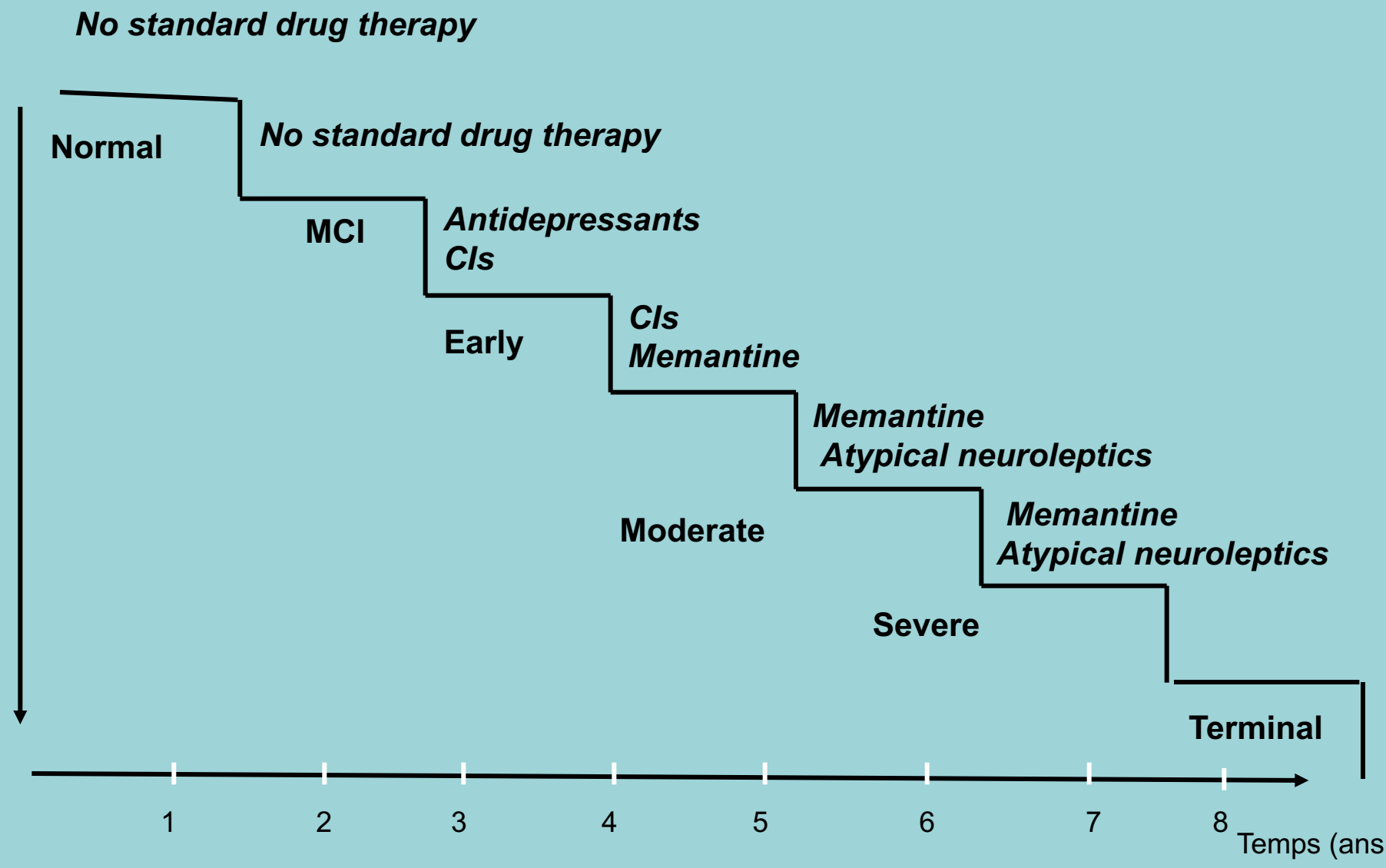


donepezil

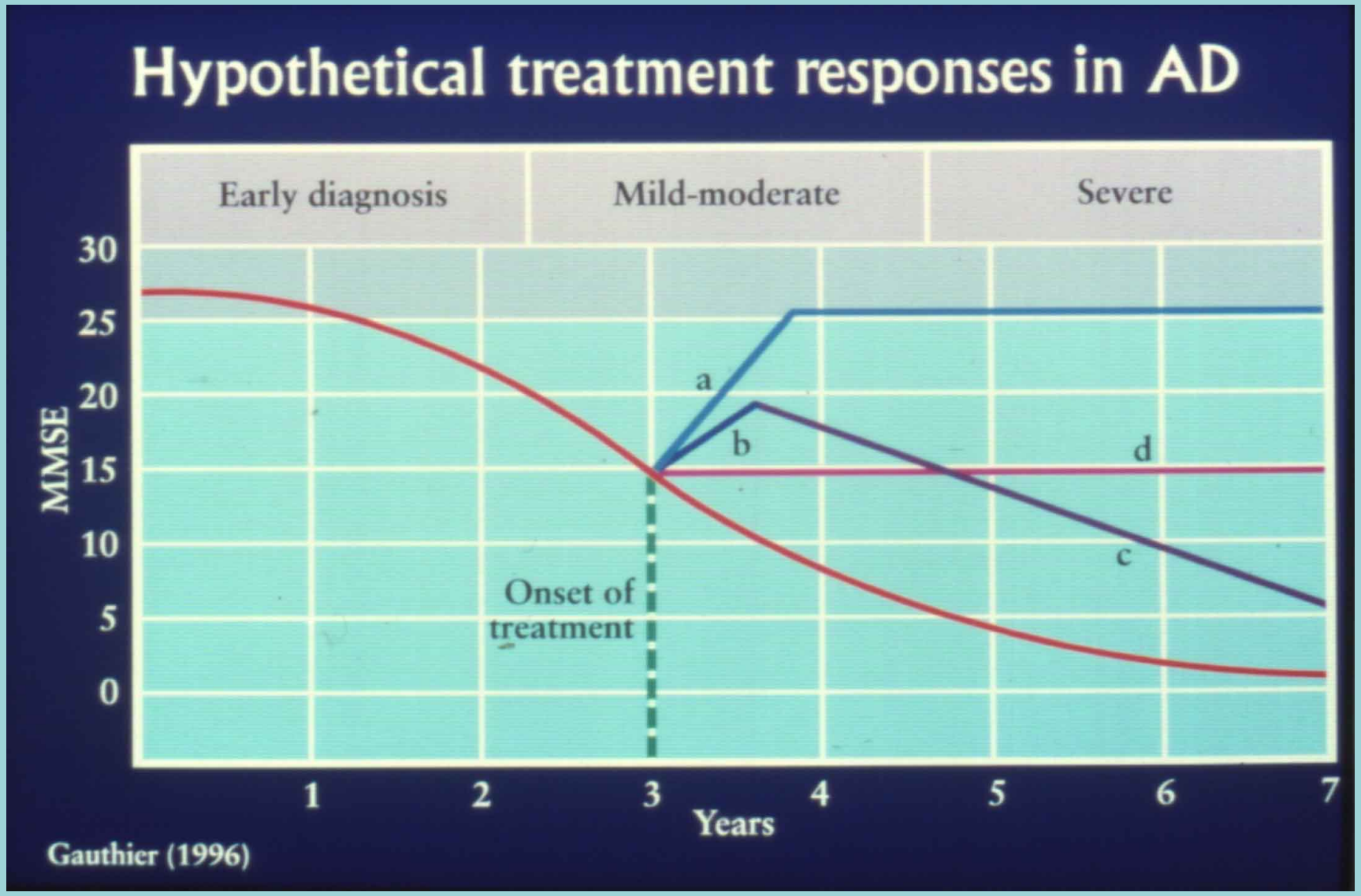
SYMPTOMATIC DRUGS FOR DEMENTIAS

- Antidepressants (ex.escitalopram)
- Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
- NMDA receptor antagonist (memantine)
- Atypical antipsychotics (risperidone, olanzapine, quetiapine)

NATURAL HISTORY OF AD AND CURRENT Rx

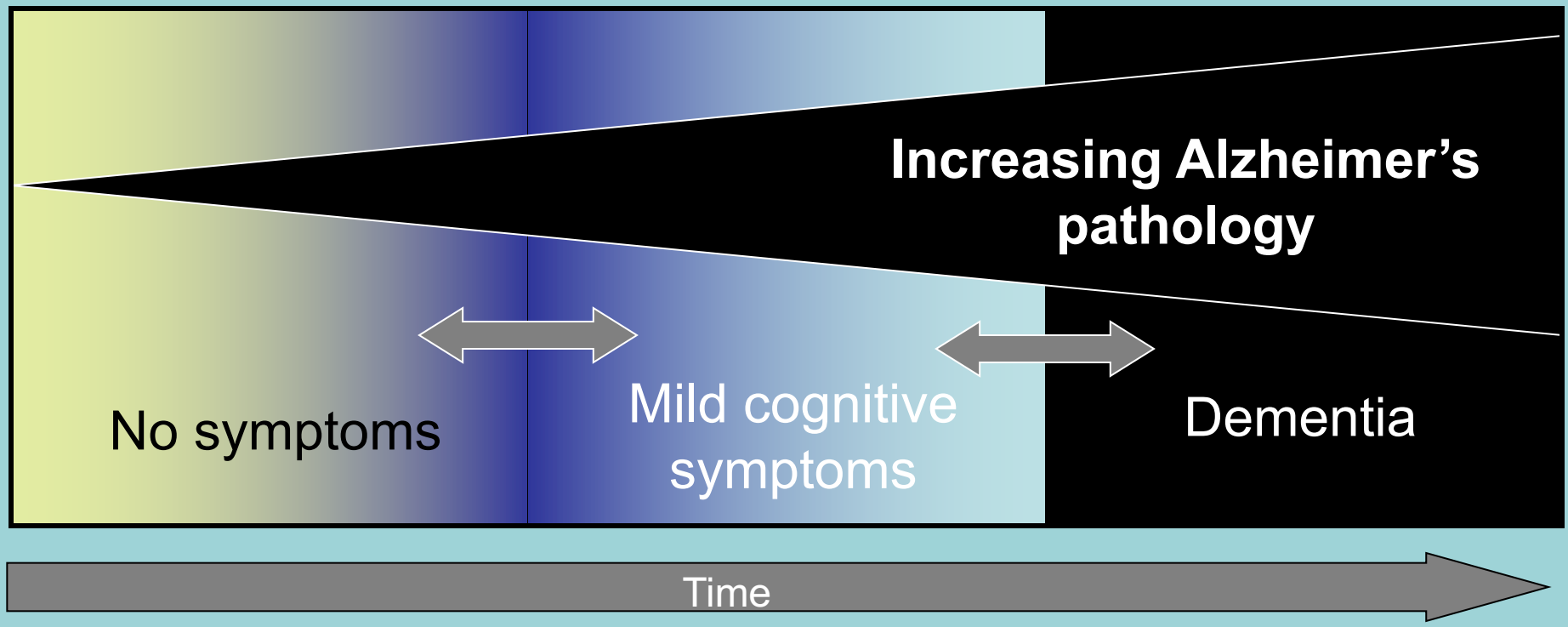


Hypothetical treatment responses in AD



Gauthier (1996)

Alzheimer's disease exists on a spectrum from minimal symptoms to dementia



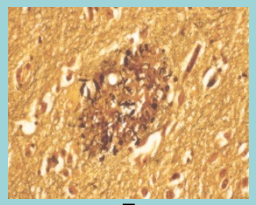
- Increasingly severe phenotype
- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

PATHOLOGIES ASSOCIATED WITH AD

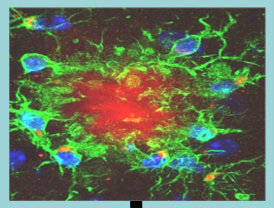
AGE

30
40
50
60
70
80
90
100

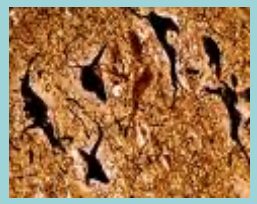
β-amyloid deposition



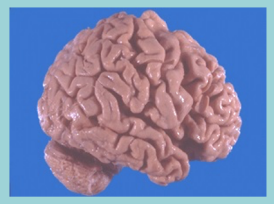
Microglial activation



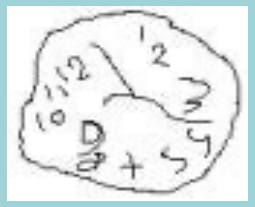
NFTs



Neuronal loss



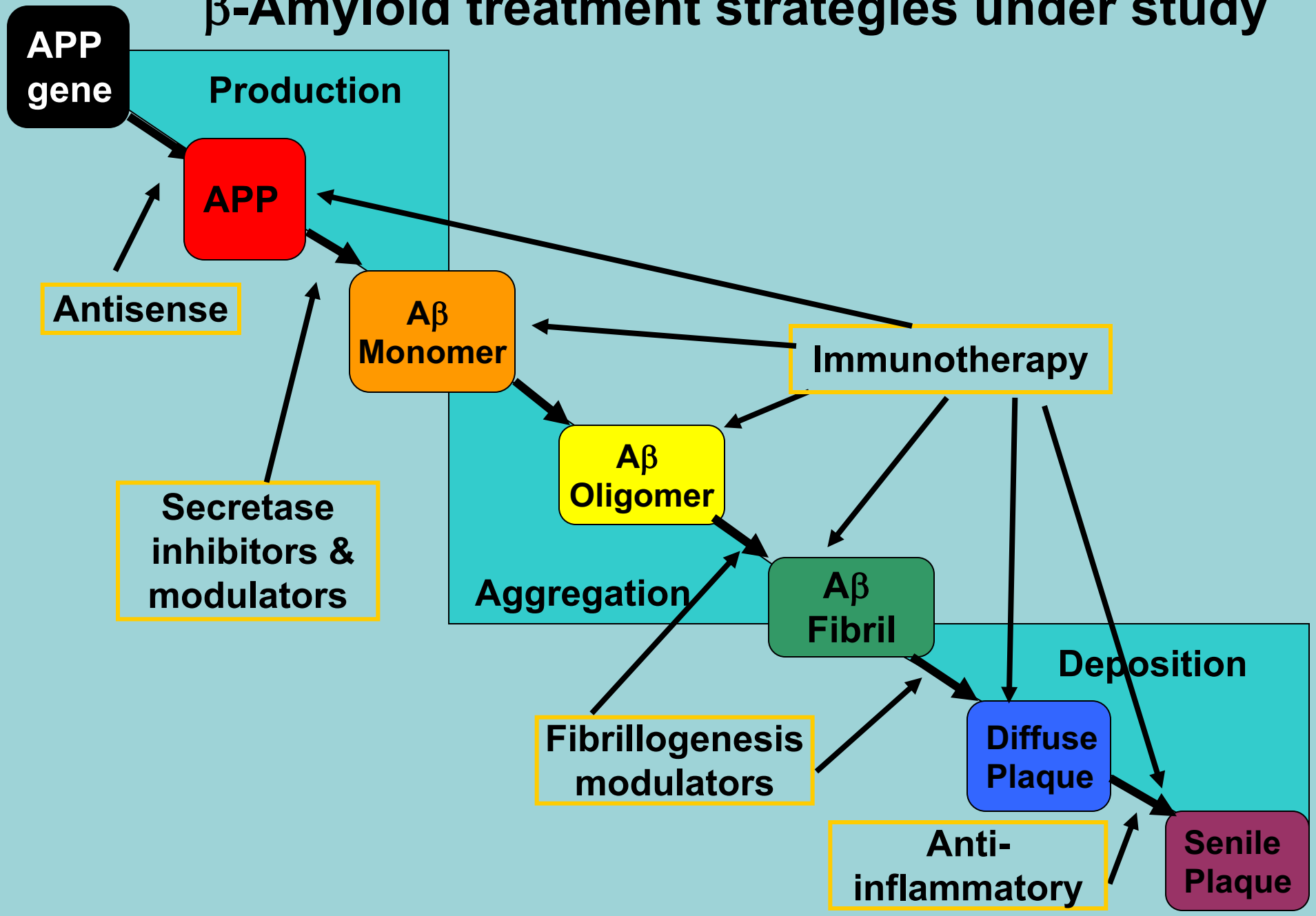
Symptoms



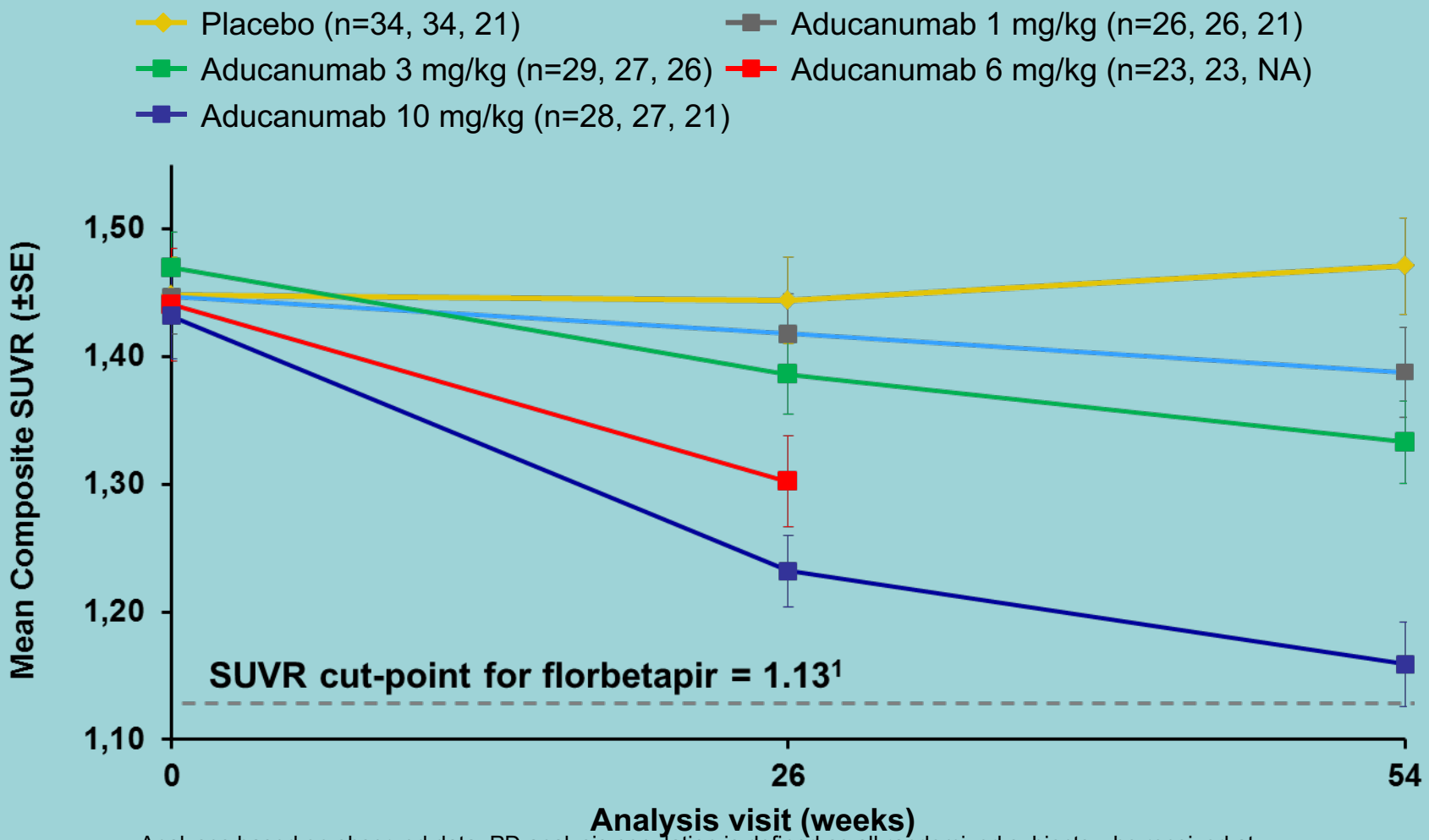
TESTABLE HYPOTHESIS

- Beta-amyloid deposition
- Tau hyperphosphorylation
- Excessive brain inflammation

β-Amyloid treatment strategies under study



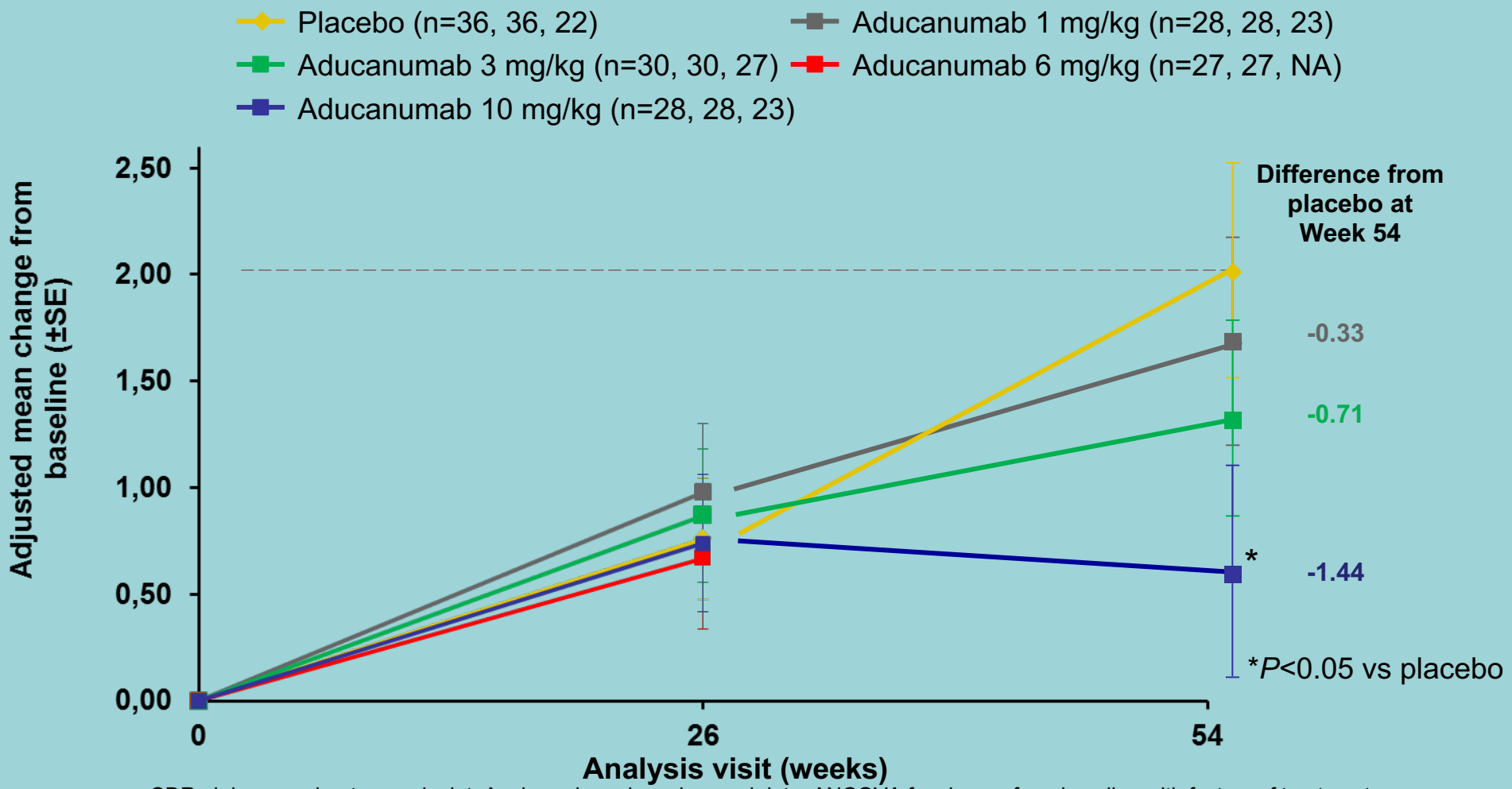
Amyloid Plaque Reduction with Aducanumab



Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

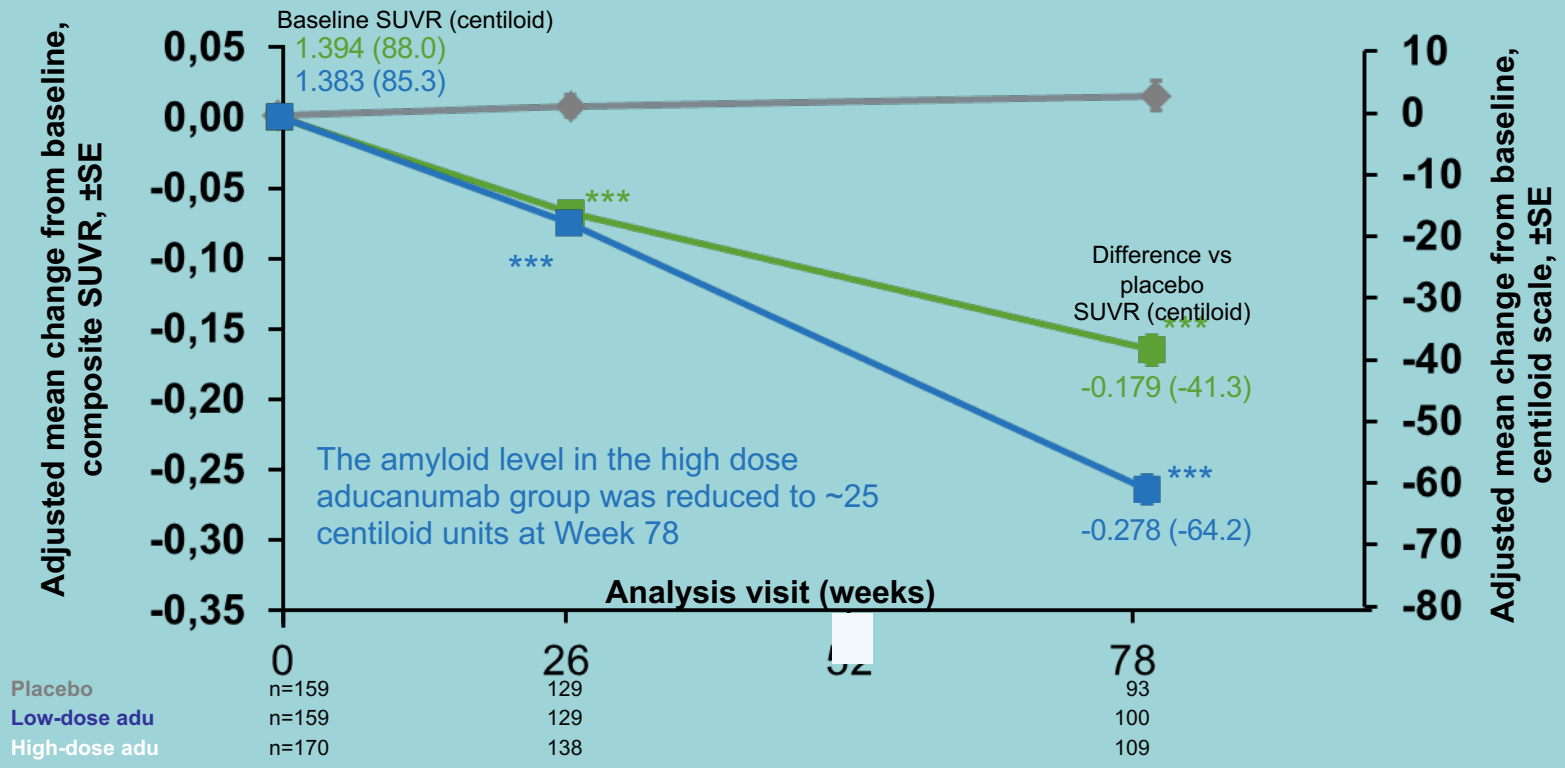
1. Landau et al. J Nucl Med 2013

Aducanumab Effect on CDR-sb



CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

EMERGE: Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab



18F-florbetapir amyloid PET analysis population. ***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from

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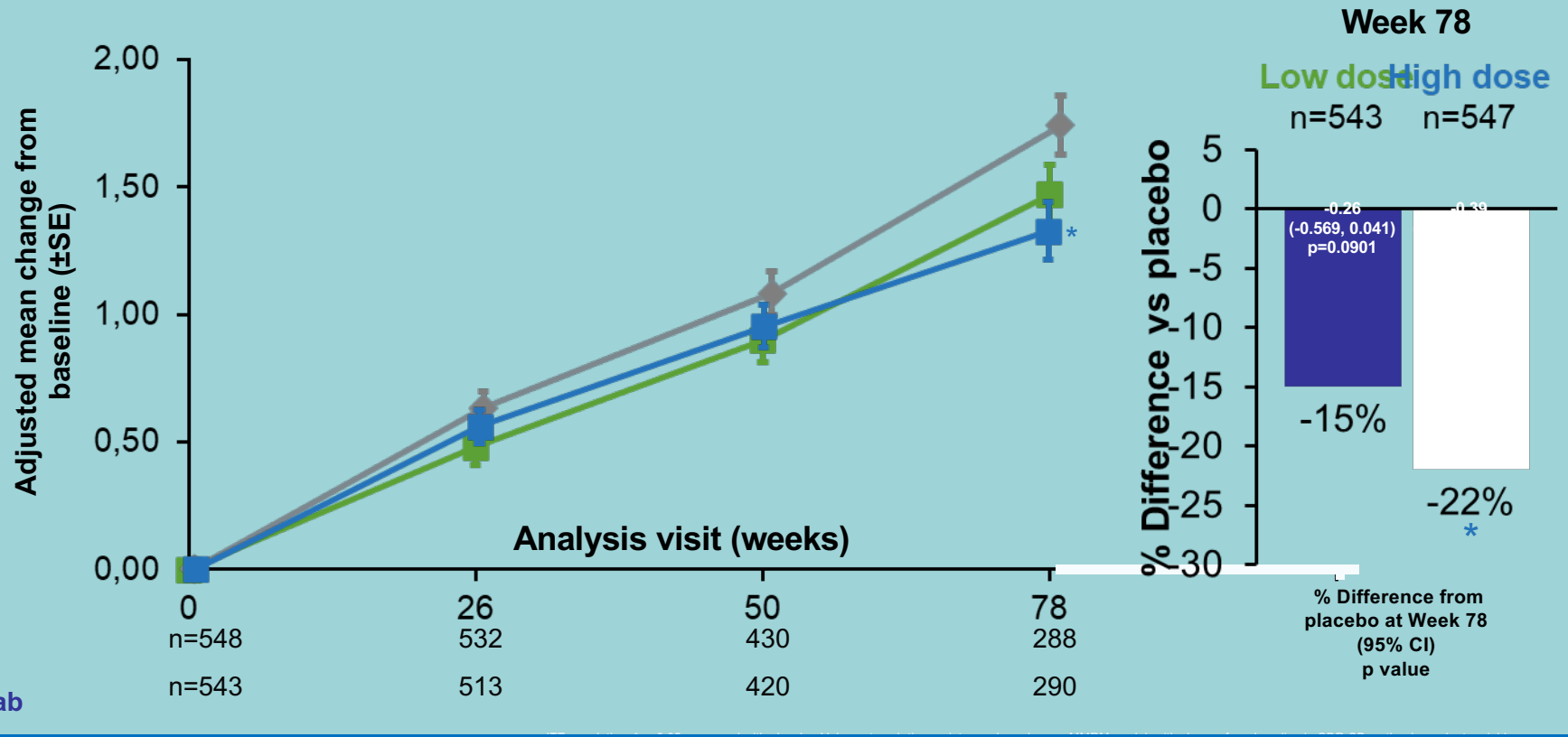
EMERGE: Longitudinal Change from Baseline in CDR-SB

The primary endpoint of change from baseline in CDR-SB at Week 78 was met



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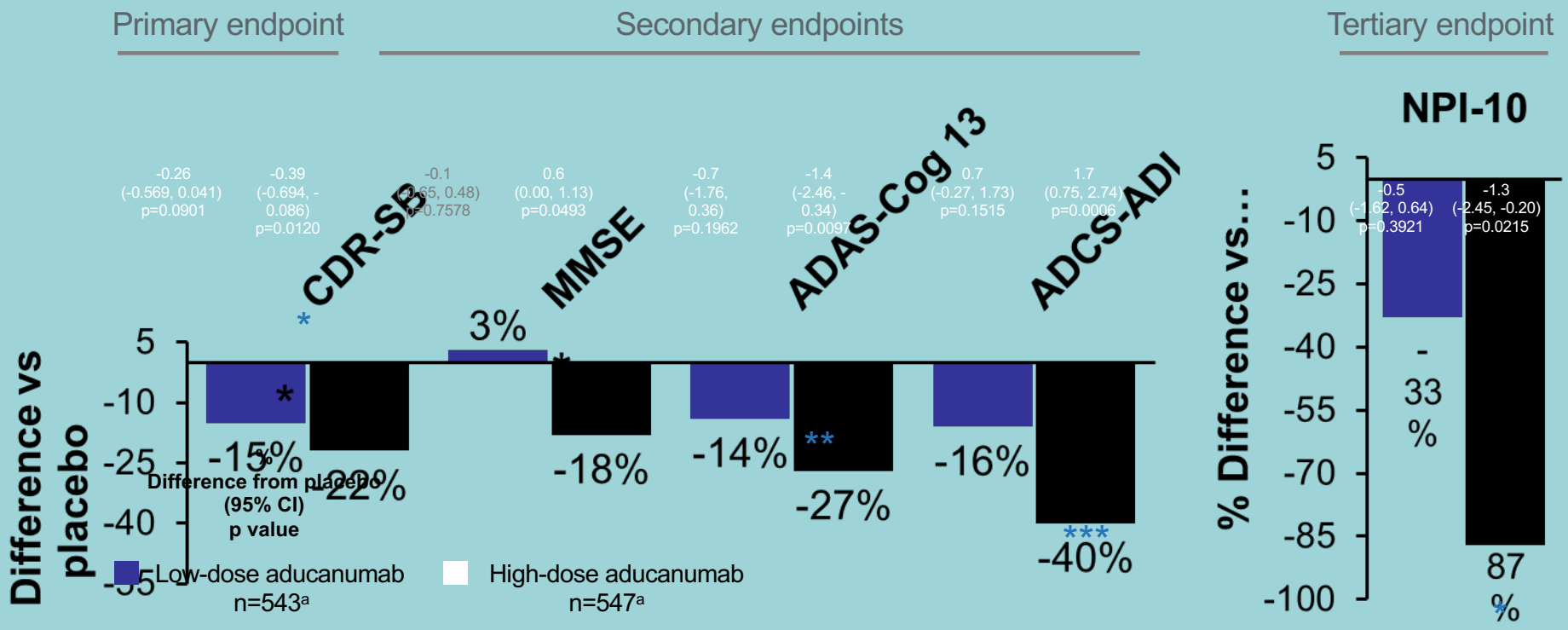
EMERGE: Clinical Endpoints at Week 78

High dose aducanumab met all clinical endpoints assessing cognition, function and behavior at Week 78



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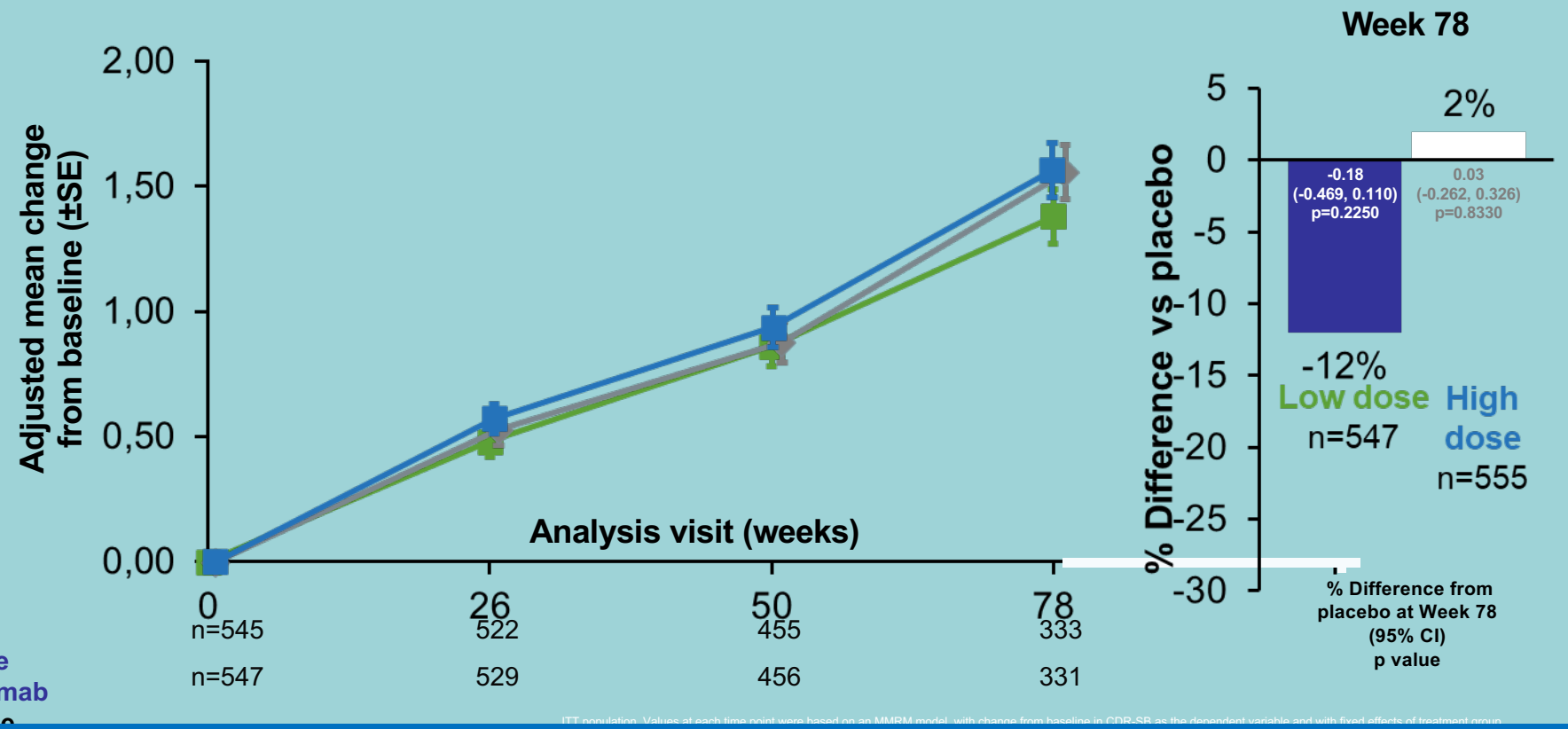
ENGAGE: Longitudinal Change from Baseline in CDR-SB

The primary endpoint of change from baseline in CDR-SB at Week 78 was not met



ITT population. Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group

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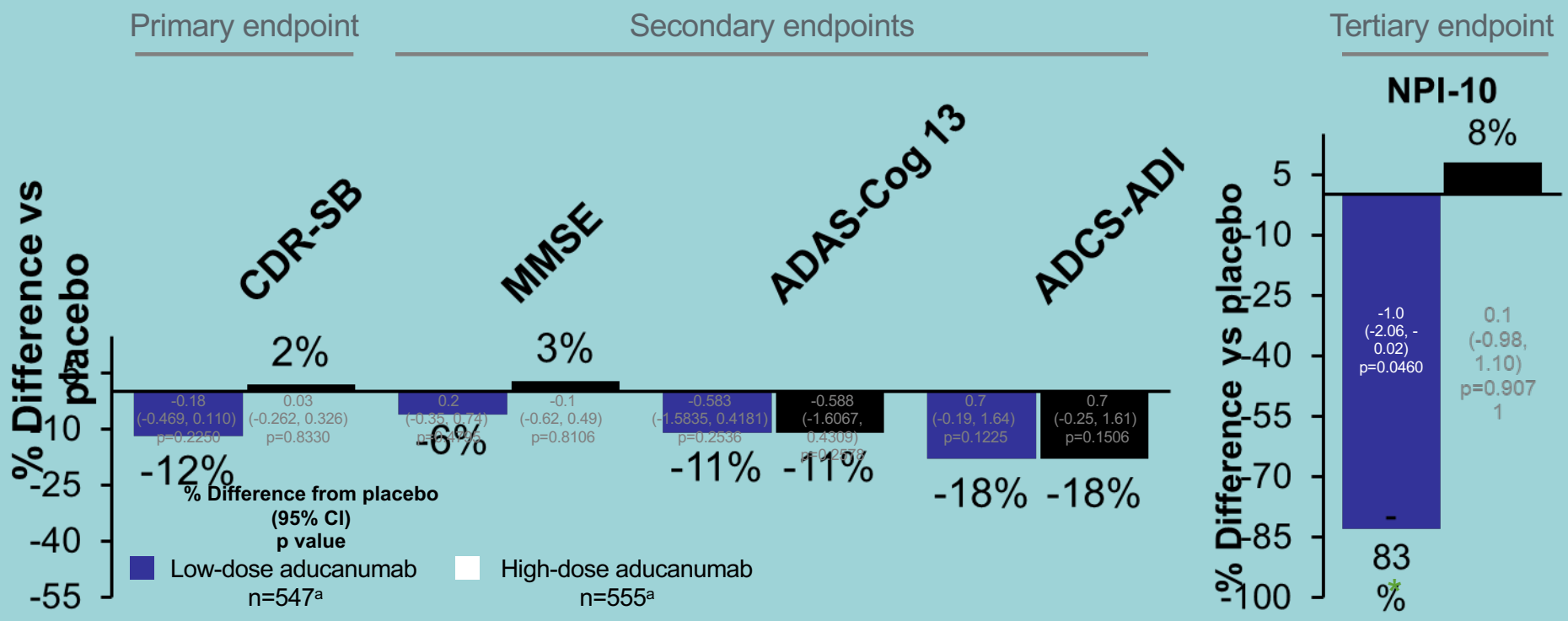
ENGAGE: Clinical Endpoints at Week 78

Results of the ENGAGE study were partially discordant with those of EMERGE



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- J. Cummings et al. Aducanumab: Appropriate Use Recommendations. J Prev Alz Dis June 20 2021.
- S. Gauthier, P. Rosa Neto. The US Expert Panel on the Appropriate Use Recommendations of Aducanumab in Clinical Practice; Commentary. J Prev Alz Dis June 20 2021.

Table 1. Clinical trial enrollment criteria and appropriate use criteria for aducanumab in clinical practice

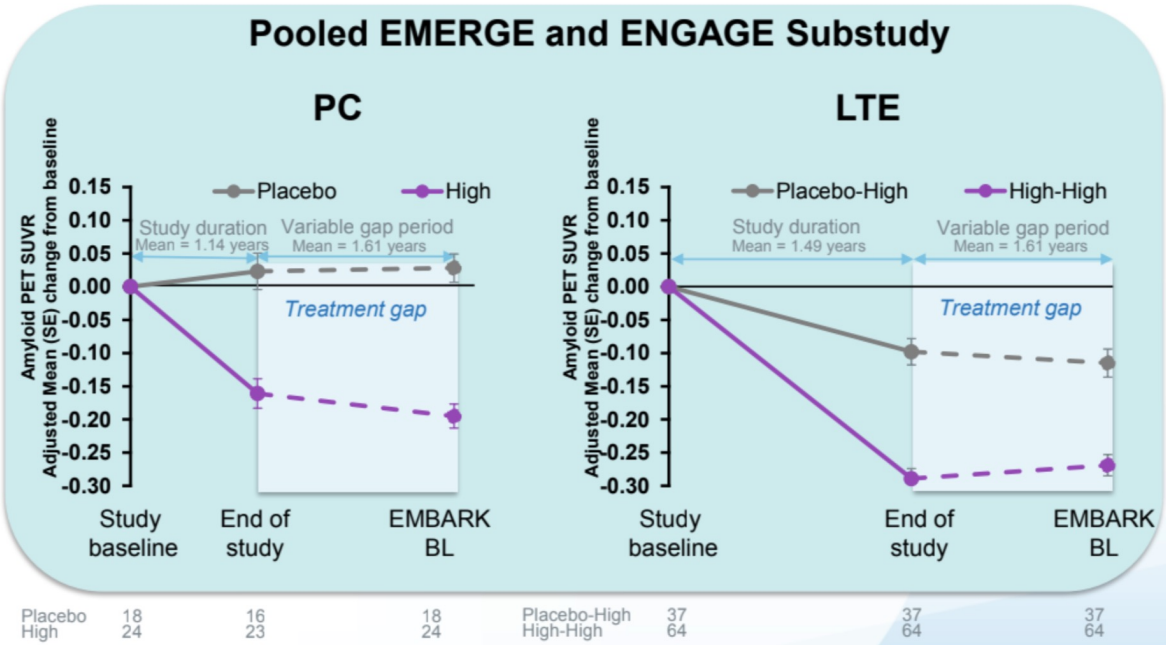
Participant Feature	Clinical Trial Enrollment Criteria	Appropriate Use in Clinical Practice
Age	50-85	Younger or older patients meeting all other criteria for treatment could be considered candidates for aducanumab
Diagnosis	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia
Scale scores at baseline	CDR Global Score 0.5; MMSE 24-30; RBANS Delayed Memory Score of 85 or less	MMSE 21-30 or equivalent such as MoCA 17-30
Amyloid status	Amyloid positive PET (visual read)	Amyloid positive PET (visual read) or CSF findings consistent with AD
Genetic testing	Consent for APOE genotyping	Genotyping should be discussed with the patient/care partner. ARIA risk should be described, and the patient's preferences assessed.
Neurological examination	Non-AD neurological disorders, stroke, and TIA excluded	Non-AD neurological disorders excluded
Cardiovascular history	Angina; myocardial infarction; congestive heart failure excluded	Stable cardiovascular conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Medical history	Excluded: clinically significant systemic illness; diabetes than cannot be managed; uncontrolled hypertension (systolic > 165; diastolic > 100); history of cancer unless in remission for 5 years or localized to skin or prostate; impaired liver function; hepatitis; HIV infection	Stable medical conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Psychiatric history	Unstable psychiatric illness in the past 6 months; alcohol or substance abuse in the past year; use of cannabinoids; positive urine tests for excluded substances	Must be stable psychiatrically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Reproductive status	Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception	Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception
Clotting status	Bleeding disorders, anticoagulants excluded	Patients on anticoagulants are excluded
Concomitant medications	Cholinesterase inhibitors and memantine allowed	Patients can be on standard of care with cholinesterase inhibitors and memantine
Baseline MRI	Baseline MRI finding that excluded participation: acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), superficial siderosis, or diffuse white matter disease	Patients should be excluded if there is evidence of acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), > 1 area of superficial siderosis, or diffuse white matter disease
Care support	Reliable informant or care partner	May be living independently or with a care partner
Informed consent	Must be signed by participant and care partner	Patient and care partner must understand the nature and requirements of therapy (e.g, monthly infusions to be performed indefinitely) and the expected outcome of therapy (slowing of decline of clinical features)

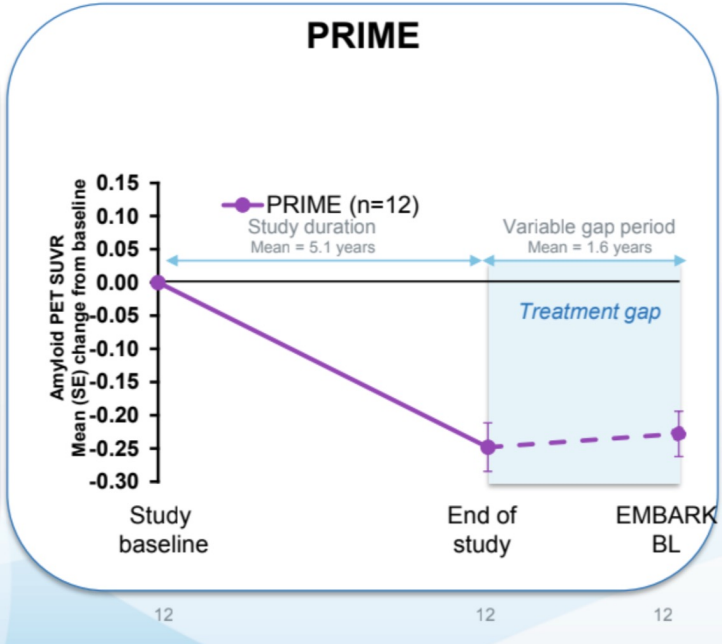
Aß – amyloid beta protein; AD – Alzheimer's disease; APOE – apolipoprotein E; CDR – Clinical Dementia Rating; cm – centimeter; CSF – cerebrospinal fluid; HIV – human immunodeficiency virus; MMSE – Mini Mental State Examination; MoCA – Montreal Cognitive Assessment; MRI – magnetic resonance imaging; PET – positron emission tomography; RBANS – Repeatable Battery for the Assessment of Neuropsychological Status; TIA – transient ischemic attack

POLLING QUESTION NO 4: TRUE OR FALSE?

The CDR-SB will be the main tool to follow patients with MCI due to AD undergoing anti-amyloid therapies.

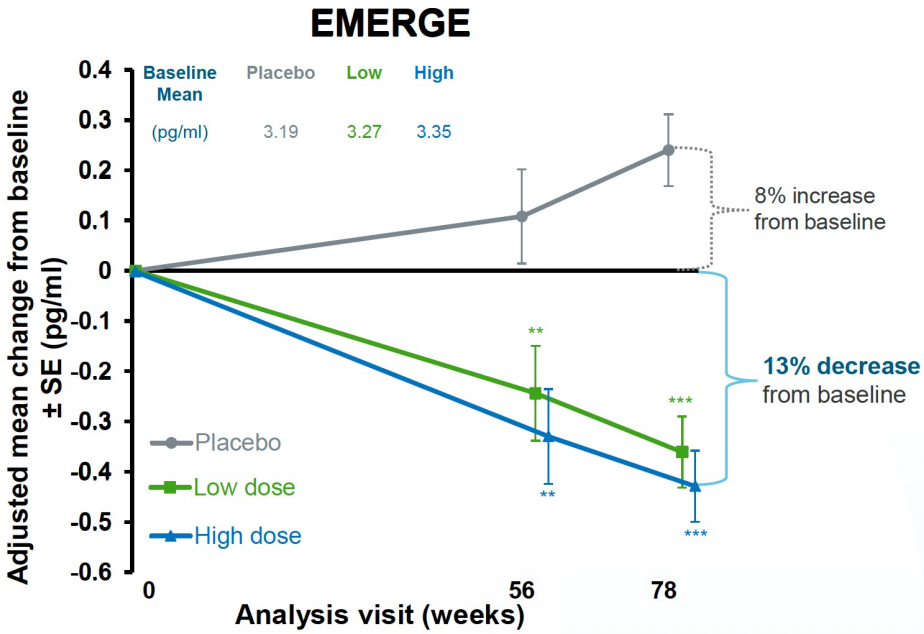
Reduction of amyloid plaque levels was maintained during the treatment gap from the end of feeder studies to EMBARK baseline: Pooled EMERGE/ENGAGE substudy data and PRIME data

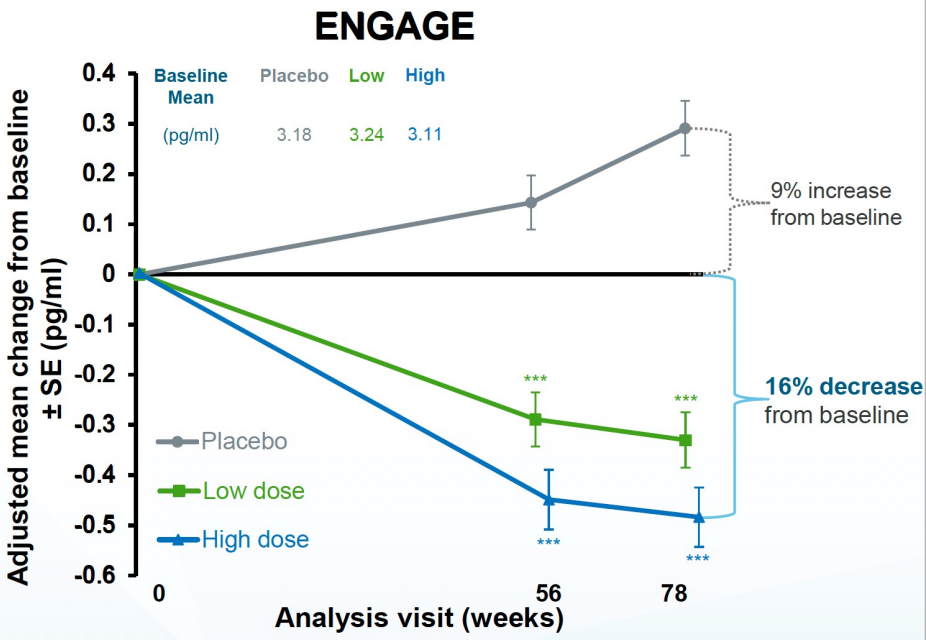




The end-of-feeder-study amyloid PET SUVR was defined as the last non-missing post-baseline amyloid PET SUVR in the feeder study. Some subjects may receive aducanumab doses after the date of the last post-baseline amyloid PET in the feeder study. For the pooled EMERGE/ENGAGE analyses, adjusted mean changes were based on an MMRM with change from feeder-study baseline amyloid PET composite SUVR as outcomes using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, feeder-study baseline SUVR value, feeder-study baseline SUVR value by time interaction, feeder-study baseline MMSE, feeder-study baseline age, and laboratory ApoE status (carrier/noncarrier). ApoE, apolipoprotein E; BL, baseline; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

Aducanumab significantly lowers plasma p-tau^{181}





Placebo	287	177	273
Low dose	293	172	269
High dose	290	168	271

Placebo	333	301	325
Low dose	331	299	322
High dose	281	242	274

*p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). **MMRM with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age, and ApoE status**. ApoE, apolipoprotein E; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SE, standard error.

EMERGING GUIDELINES FOR ANTI-AMYLOID DRUGS - 1

- They would help in ‘early AD’ (MCI and mild dementia due to AD, e.g. A+)
- They need high doses with risk of ARIA (brain swelling and micro bleeds)
- They may have downstream effect on tau pathological spread

EMERGING GUIDELINES FOR ANTI-AMYLOID DRUGS -

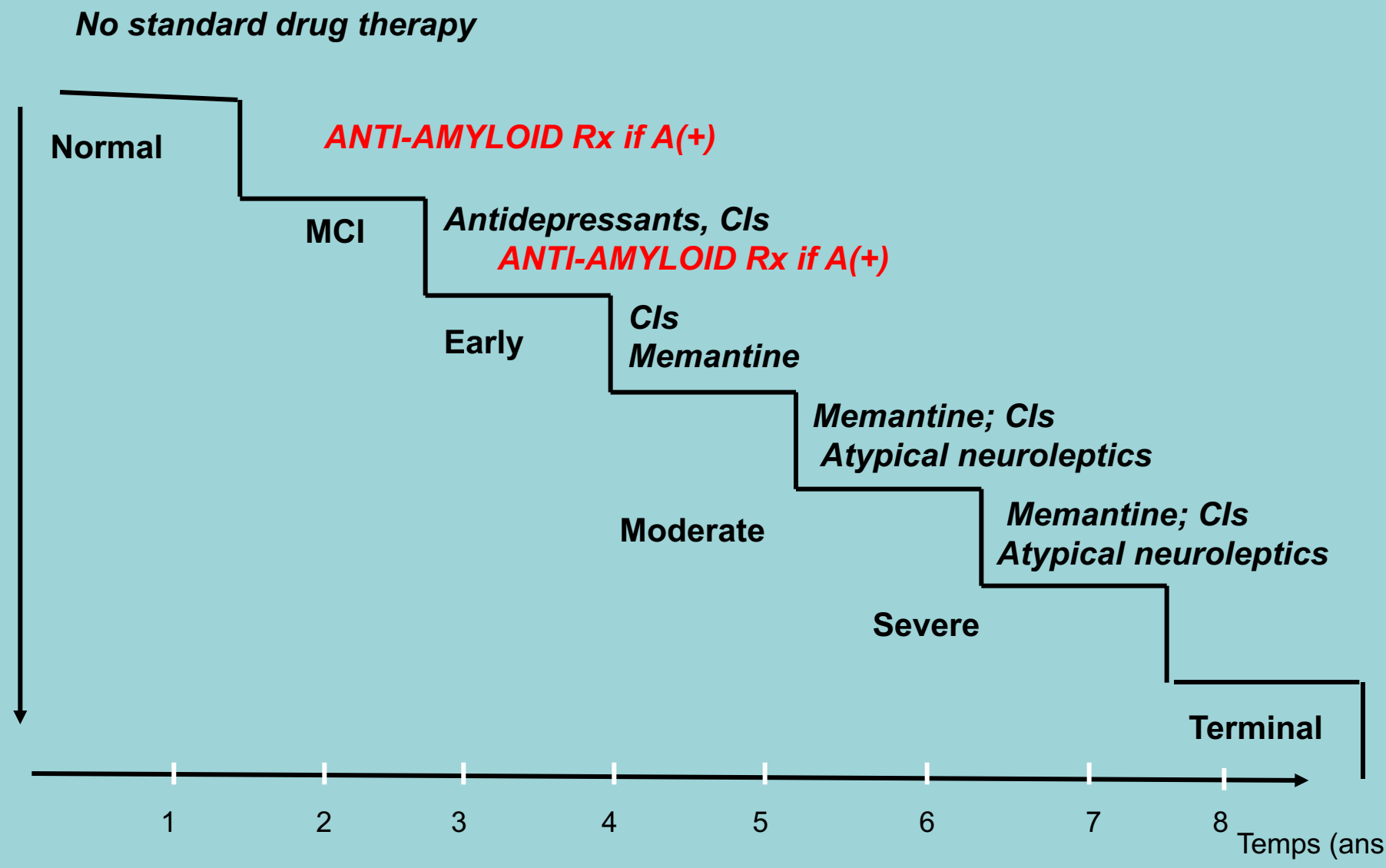
- It may be possible to stop the Rx after reaching A- as demonstated by PET, CSF or plasma ptau
- They should be stopped when reaching moderate dementia, which may be operationally defined as CDR-global 2, MMSE below 19, loss of IADL.

POLLING QUESTION NO 4: TRUE OR FALSE?

The CDR-SB will be the main tool to follow patients with MCI due to AD undergoing anti-amyloid therapies.

FALSE

NATURAL HISTORY OF AD AND CURRENT Rx



CONCLUSIONS

- The diagnosis of MCI and dementia due to AD is becoming biological but should done in symptomatic people with demonstrated cognitive decline
- The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments – possibly a golden age for remote cognitive screening for MCI
- MCI due to AD has become a target for disease modifying therapies and will require in-person and remote cognitive & functional follow-up

REFERENCES

- Tsoy E, Zygouris S, Possin KL. Current state of self-administered brief computerized cognitive assessments for detection of cognitive disorders in older adults: a systematic review. J Prev Alz Dis 2021;3(8):267-276

- Nosheny et al. Validation of online functional measures in cognitively impaired older adults. Alzheimer's Dement 2020;16:1426-1437

- Li et al. Concordance between the clinical and the electronic CDR. J Prev Alz Dis 2021;8(S1):S30-31